REMARKS

Claims 1-20 and 23-27 are pending in this application and have been rejected. Applicants thank the Examiner for withdrawal of the previous rejection under 35 U.S.C. § 112, first paragraph, in view of Applicants' amendment and response filed May 28, 2003. Applicants respectfully request consideration and examination of this application and the timely allowance of the pending claims in view of the arguments below.

Claim Rejections under 35 U.S.C. § 102(e) in view of *Cummings*

Claims 1-4, 8-13, 16-18, and 23-27 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,464,778 to Cummings *et al.* (hereafter "*Cummings*"). The Examiner alleges that "the claimed structural limitations (SEQ ID NO: 2 and P-selectin binding domains thereof) and the claimed functional limitations (e.g., inhibiting when the thrombus inducing agent is LTC_4) would have been inherent properties of the referenced methods of treating various acute and chronic conditions associated with thrombosis . . . at the time the invention was made." Office Action at page 4.

The Examiner further states that "Cummings et al. teach the use of PSGL in the treatment of acute and chronic conditions associated with leukocyte adherence, inflammation and coagulation, including ischemia-reperfusion injury and atherosclerosis (see column 18, paragraphs 5-8; columns 19-20). Cummings et al. teach the properties and the use of PSGL (column 9-18) including protein fragments thereof (e.g. column 20, paragraph 3)." (Office Action at page 3, emphasis in original).

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Additionally, the Examiner stated: "Cummings further teaches a number of clinical disorders associated with ischemia reperfusion (column 19, paragraph 6) that are associated with therapeutic endpoints, which include the inhibition of thrombosis as a therapeutic endpoint." (Office Action at page 3).

Applicants respectfully traverse this rejection. Applicants' claims are directed to a method of treating or inhibiting thrombosis in a subject by administering a composition comprising an effective amount of a PSGL-1 protein to the subject.

It appears that the Examiner is alleging that thrombosis is a clinical manifestation of the diseases (particularly ischemia-reperfusion injury, coagulation diseases, and atherosclerosis) described in *Cummings* and, as such, *Cummings* inherently anticipates the claimed methods of treating or inhibiting thrombosis using PSGL-1.

Applicants submit that the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. Applicants submit that the thrombosis is merely a possible manifestation of the diseases discussed in *Cummings*, and is not necessarily present each time PSGL is administered to treat one or more of the diseases discussed in *Cummings.* Thus, it is not clear that *Cummings* always results in the treatment or inhibition of thrombosis.

Cummings discusses that P-selectin has several functions relating to leukocyte adherence, inflammation, tumor metastases, and coagulation and speculates on the use of a P-selectin ligand to modulate these conditions. *See* column 18, lines 34-39. *Cummings*, however, fails to specifically comment on the role of P-selectin or a PSGL-1 protein in thrombosis, i.e., formation and development of a thrombus within a blood

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vessel. Additionally, *Cummings* does not disclose movement of cells relative to blood vessels or suggest that such movement would be increased by administration of a PSGL-1 protein, as recited in claim 23. Further, *Cummings* also does not provide any teaching of a thrombus-inducing agent including LTC_4, or that thrombus formation induced by a thrombus-inducing agent would be inhibited by administration of a PSGL-1 protein, as recited in claim 25.

Applicants had previously provided the *Eppihimer* reference to substantiate Applicants' arguments and as evidence to show that while a specific composition may inhibit thrombosis, it does not necessarily inhibit an alleged thrombosis-associated condition, and therefore, that property is not an inherent property of that composition. The Examiner, however, appears to not be convinced by that argument and alleges that "*Eppihimer* does disclose the immunoneutralization of P-selectin with PSGL does result in the reduction of thrombus-formation." Office Action at page 5.

Applicants submit that the Examiner has not properly characterized the *Eppihimer* reference. Contrary to the Examiner's allegation, the discussion in *Eppihimer* in fact fully supports Applicants argument. For example, the discussion in *Eppihimer* in fact recites the following at page 2487.

> "[I]mmunoneutralization of P-selectin with rPSGL-Ig compared with vehicle, also resulted in reduction in . . . thrombus-formation, with no effect on leukocyte accumulation. These results agree favourably with the present study, in which early leukocyte adhesion and transmigration were not reduced with treatment of rPSGL-Ig, but thrombosis was inhibited."

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Thus, while *Eppihimer* discusses that thrombosis was inhibited by r-PSGL-Ig, *Eppihimer* clearly provides evidence for the fact that that had no effect on the alleged thrombosis-associated conditions, thus consistent with Applicants arguments in this and the previous response.

Accordingly, Applicants submit that claims 1-4, 8-13, 16-18, and 23-27 are not inherently anticipated by *Cummings* and request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 102(e) in View of *Larsen*

Claims 1-5, 7-18, and 23-27 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,840,679 to *Larsen et al* ("*Larsen*"). The Examiner has maintained his rejection over *Larsen* from the first Office Action, in which he alleged that "the claimed structural limitations (SEQ ID NO: 2 and P-selectin binding domains thereof) and the claimed functional limitations (e.g. inhibiting wherein the thrombus inducing agent is LTC_4) would have been inherent properties of the referenced methods of treating various conditions associated with thrombosis with PSGL and fragments thereof . . . at the time the invention was made." (Office Action at page 6).

The Examiner further elaborated on this rejection, stating: "Again, applicant is invited to note that the prior art teachings are directed to the same or nearly the same conditions as targeted by the instant specification (e.g. myocardial infarction), to the same or nearly the same mechanism of action (e.g. inhibiting P-selectin mediated intercellular adhesion) as targeted by the instant specification[.]" Office Action at page 5.

According to the Examiner, [e]ven though the claims include underlying mechanisms or physiology which contribute to thrombosis, the claims do not appear to

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distinguish the prior art teaching the same or nearly the same methods to achieve the same end results. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious." (Office Action at page 5.)

It appears that the Examiner is once again contending that a mere fact that PSGL has been suggested to be beneficial for the treatment of certain conditions, that it will necessarily lead to the inhibition or treatment of thrombosis. Applicants submit that a recitation of conditions that may be associated with thrombosis, does not teach or suggest that a treatment that will work for those conditions will necessarily work for thrombosis. As discussed above, PSGL will not necessarily lead to the inhibition or treatment of thrombosis each time it is administered for the treatment of one or more of the conditions discussed in *Larsen* because thrombosis will not necessarily be present in individuals being treated for one or more of the conditions discussed in *Larsen*.

In fact, as discussed above, *Eppihimer* clearly shows that a PSGL composition that inhibits thrombosis does not necessarily inhibit the allegedly associated conditions, i.e., leukocyte adhesion and inflammation. *Eppihimer* at 2486 and 2487.

Applicants' claimed invention is directed to the inhibition or treatment of thrombosis using PSGL. *Larsen* only speculates on the use of an isolated P-selectin ligand protein in treating conditions characterized by P-selectin-mediated intercellular adhesion including myocardial infarction, bacterial or viral infection, metastatic conditions etc. (*see* column 15, lines 50-66). Although, *Larsen* suggests combining P-selectin ligand protein with other factors, including thrombolytic or anti-thrombotic

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factors (*see* column 16, lines 27-29), *Larsen* does not teach treatment or inhibition of thrombosis by administering a composition comprising a PSGL-1 protein. Indeed, *Larsen* fails to teach that PSGL-1 protein itself has anti-thrombic activity. In fact, these statements in *Larsen* are **teaching away** from the claimed invention by suggesting that different agents should be administered to treat or inhibit thrombosis. Additionally, *Larsen* fails to disclose movement of cells relative to blood vessels or that such movement would be increased by administration of a PSGL-1 protein. *Larsen* also does not identify a thrombus-inducing agent or teach inhibition of thrombus formation induced by a thrombus-inducing agent by administration of a PSGL-1 protein.

In view of the foregoing, Applicants submit that *Larsen* does not inherently anticipate the claimed invention as it is not clear that *Larsen* always results in the treatment or inhibition of thrombosis. Accordingly, Applicants submit that claims 1-5, 7-18, and 23-27 are in condition for allowance and request entry as such.

Claim Rejections under 35 U.S.C. § 103(a) in View of *Maugeri*

Claims 1-20 and 23-27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over *Cummings* and *Larsen* and in further evidence of *Maugeri* et al., Thrombosis and Haemostasis 72: 450-456 (1994) (hereafter "*Maugeri*"). The Examiner again maintained his rejection from the first Office Action, which stated: "given the teachings of Cummings and Larsen to inhibit PSGL-1-mediated interactions and inflammatory responses, including those associated with coronary/thrombotic conditions, the ordinary artisan would have had a reasonable expectation of success at the time the invention was made to treat or inhibit thrombosis, to increase the

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movement of cells relative to blood vessels and to inhibit the effect of thrombus-inducing agents. . . ." Paper No. 14, at 8.

The Examiner elaborated on this rejection, stating: "Applicant acknowledges that *Maugeri* teaches the role of P-selectin in the synthesis of LTC_4 and that an anti-P-selectin antibody inhibited leukocyte-platelet interaction and reduced synthesis of LTC_4." (Office Action at page 7.)

Applicants respectfully traverse this rejection. Applicants submit that the Examiner has improperly combined *Cummings*, *Larsen* and *Maugeri* by improperly characterizing conditions "associated with thrombotic conditions" that are discussed in *Cummings* and *Larsen* as being the same as "thrombotic conditions," and by further alleging that PSGL would work for the treatment of thrombosis simply because it may be used for treating certain allegedly thrombosis-associated conditions. Further, Applicants submit that the Examiner has improperly inferred from *Maugeri* that just because an anti-P-selectin antibody inhibited leukocyte-platelet interaction and reduced the synthesis of a thrombus-inducing agent, such as LTC_4, that PSGL-1 would work for inhibition or treatment of thrombosis. *See* Office Action at pages 8 and 9.

As discussed above, *Cummings* and *Larsen* do not inherently anticipate the claimed invention as it is not clear that the use of PSGL for the treatment of conditions described in *Cummings* and *Larsen* always results in the treatment or inhibition of thrombosis, as thrombosis may not even be present in the conditions that are described in *Cummings* and *Larsen*. Applicants submit that a mere possibility that thrombosis

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may be associated with some of these conditions, does not mean that thrombosis will be necessarily present, and therefore be inhibited or treated by PSGL.

Maugeri, despite illustrating the role of P-selectin in the synthesis of LTC_4, does not compensate for this deficiency. While *Maugeri* discusses that a P-selectin antibody can inhibit the synthesis of LTC_4, it fails specifically to disclose a soluble PSGL-1 protein or suggest that PSGL-1 will work for the inhibition or treatment of thrombosis. *Maugeri* only posits that polymorphonuclear leukocyes and platelets cooperate in processing arachidonic acid-derived intermediate metabolites into biologically active substances that play a pathophysiological role in inflammation and thrombosis, and further that LTC_4 may be produced in this system (*See Maugeri* at 450).

In view of the foregoing, Applicants submit that there is no motivation to combine *Maugeri*, which teaches the inhibition of LTC_4 with an antibody to P-selectin, with *Cummings* and *Larsen* which discuss the use of PSGL for the treatment or inhibition of certain allegedly thrombosis-associated conditions. Further, even if they were combined, not only the combination fail to teach all the limitations of the claimed invention, but there is no motivation to expect that while PSGL may work for certain allegedly thrombosis-associated conditions, that it will necessarily work for inhibition of thrombosis or a thrombus-inducing agent.

Thus, Applicants request that this rejection of claims 1-21 and 23-27 under 35 U.S.C. § 103(a) be reconsidered and withdrawn and request entry as such.

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Claim Rejections under 35 U.S.C. § 103(a) in View of *Johnston*

Claims 25-27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over *Cummings* and *Larsen* as applied to claims 1-27 above and in further evidence of *Maugeri* and *Johnston et al.* (J. Immunol. 159:4514-4523, 1997) (hereafter "*Johnston*"). The Examiner is alleging that, "[O]ne of ordinary skill in the art would have expected that the methods of treating thrombotic conditions taught by *Cummings* and *Larsen* would have inhibited the thrombus inducing agent in a subject, including LTC_4 at the time the invention was made. Further both *Maugeri* and *Johnston* teach that inhibiting P-selectin-mediated events results in the inhibition of thrombus-inducing biological substances, including LTC_4." (Paper No. 14, at 9.)

The Examiner further alleged that "Given the teachings of Cummings and Larsen to inhibit PSGL-1-mediated interactions and inflammatory responses . . . the ordinary artisan would have had a reasonable expectation of success at the time the invention was made to treat or inhibit and to inhibit the effect of thrombus-inducing agents . . . ." (*Id.*)

Applicants claimed invention, as recited in claim 25, is directed to a method for inhibiting thrombus formation induced by a thrombus-inducing agent in a subject by administering an effective amount of a soluble PSGL-1 protein or fragment. Applicants submit that none of *Cummings*, *Larsen*, *Maugeri or Johnston*, alone or in combination, teach each and every limitation of the claimed invention.

As discussed above, *Cummings* discusses the role of P-selectin in leukocyte adherence, inflammation, tumor metastases, and coagulation, including ischemia-

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reperfusion injury and atherosclerosis and further suggests that a P-selectin ligand may be used for modulating these event. *Cummings,* however, fails to disclose the role of P-selectin or PSGL in thrombosis or the treatment or inhibition of thrombosis by administering a PSGL-1 protein to a subject. Additionally, *Cummings* also fails to disclose a thrombus-inducing agent, or inhibiting thrombus formation induced by such an agent by administering a PSGL-1 protein.

Also, as discussed above, *Larsen* teaches the use of isolated PSGL in the treatment of various diseases mediated by P-selectin intercellular adhesion, however, *Larsen* fails to teach treatment or inhibition of thrombosis using a PSGL protein. Additionally, also as acknowledged by the Examiner, *Larsen* fails to disclose a thrombus-inducing agent or that thrombus formation induced by a thrombus-inducing agent would be inhibited by administration of a PSGL protein.

Thus, it is not clear from *Cummings* and *Larsen* that while PSGL may be used for the treatment of allegedly thrombosis-associated conditions, that it will necessary work for the treatment of thrombosis, as thrombosis may not even be present.

Maugeri and *Johnson*, despite illustrating the role of P-selectin in the synthesis of LTC_4, do not compensate for this deficiency.

As discussed above, *Maugeri* only discusses that a P-selectin antibody (and not PSGL) can inhibit the synthesis of LTC_4. Whereas *Maugeri* posits that polymorphonuclear leukocyes and platelets cooperate in processing arachidonic acid-derived intermediate metabolites into biologically active substances that play a pathophysiological role in inflammation and thrombosis, and further that LTC_4 may be

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produced in this system (*See Maugeri* at 450), *Maugeri* does not explicitly teach that LTC_4 is a thrombus-inducing agent. Applicants submit that even if *Maugeri* had explicitly characterized LTC_4 as a thrombus-inducing agent, there is no teaching or suggestion in *Maugeri* that thrombus formation induced by LTC_4 would be inhibited by administration of a PSGL-1 protein.

Therefore, none of *Cummings*, *Larsen* or *Maugeri*, alone or in combination, teach or suggest inhibiting thrombus formation induced by a thrombus-inducing agent in a subject by administration of a PSGL-1 protein.

Johnston does not cure the deficiencies of *Cummings*, *Larsen* and *Maugeri*, alone or in combination. Specifically, *Johnston* teaches that in case of LTC_4-induced acute inflammation, there is an increase in leukocyte rolling flux, a decrease in leukocyte rolling velocity, and an increase in leukocyte adhesion. *Johnston*, further teaches that the increase in leukocyte rolling flux, decrease in leukocyte rolling velocity, and increase in leukocyte adhesion were reversed by a P-selectin antibody. However, *Johnston* fails to disclose a PSGL-1 protein and also does not teach or suggest that LTC_4 is a thrombus-inducing agent. Further, even if *Johnston* had taught that LTC_4 is a thrombus-inducing agent, there is no teaching or suggestion in *Johnston* that a composition that may inhibit conditions associated with LTC_4-induced inflammation will have any effect on thrombosis or thrombus-formation induced by LTC_4. In fact, Applicants' argument is further substantiated by *Eppihimer et al.* who have shown that a specific composition that inhibits thrombosis does not necessarily inhibit the alleged thrombosis-associated conditions, namely, cellular adhesion and inflammation.

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Therefore, one of ordinary skill in the art could not reasonably have drawn an inference based on *Johnston* that an agent that induces inflammation would also induce thrombosis, or a composition that reverses a condition associated with LTC_4 induced inflammation would have any effect on LTC_4 induced thrombosis.

Therefore, none of *Cummings*, *Larsen*, *Maugeri,* or *Johnston*, alone or in combination, teach or suggest a method of inhibiting thrombus formation induced by a thrombus-inducing agent by administering a PSGL-1 protein.

In view of the foregoing, Applicants request that this rejection be withdrawn and submit that claims 25-27 are in condition for allowance.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and withdrawal of the rejections and the timely allowance of the pending claims. Should the Examiner not believe that the claims are in condition for allowance, Applicants request that she please contact their undersigned representative at (202) 408-4086 for an interview to discuss the application.

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Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: November 26, 2003

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